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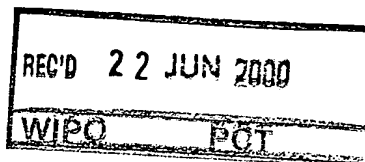
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INVESTOR IN PEOPLE

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Cardiff Road
Newport
South Wales
NP10 8QQ

10/009008

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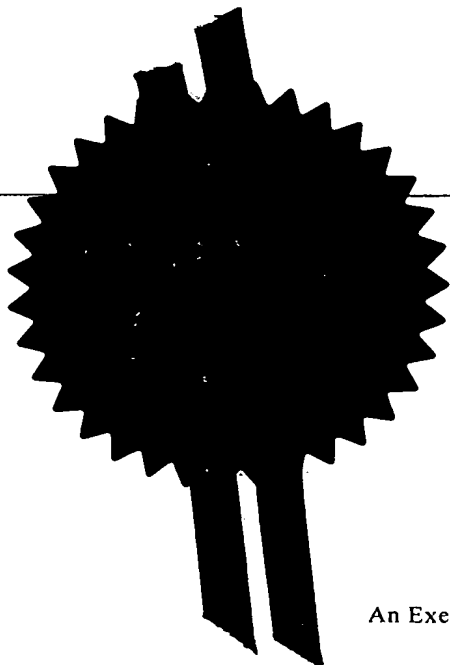
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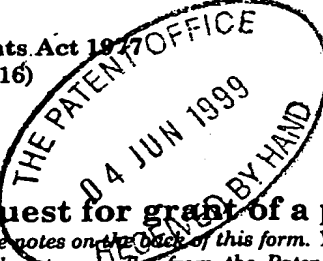
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Patents Form 1/77

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1/77

Request for grant of a patent

(See the notes on the back of this form. You can also get an explanatory leaflet from the Patent Office to help you fill in this form)

The Patent Office

Cardiff Road

Newport

Gwent NP9 1RH

1.	Your reference	GB Case	4-30970/P1/HO 17
2.	Patent application number (The Patent Office will fill in this part)	9913083.3	
3.	Full name, address and postcode of the or of each applicant (underline all surnames)	NOVARTIS AG SCHWARZWALDALLEE 215 4058 BASEL SWITZERLAND	
	Patent ADP number (if you know it)	7125487002	
	If the applicant is a corporate body, give the country/state of its incorporation	SWITZERLAND	
4.	Title of invention	Organic Compounds	
5.	Name of your agent (If you have one) "Address for service" in the United Kingdom to which all correspondence should be sent (including the postcode)	B.A. YORKE & CO. CHARTERED PATENT AGENTS COOMB HOUSE, 7 ST. JOHN'S ROAD ISLEWORTH MIDDLESEX TW7 6NH	
	Patents ADP number (if you know it)	1800001	
6.	If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and (if you know it) the or each application number	Country	Priority application number (if you know it)
			Date of filing (day/month/year)
7.	If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application	Number of earlier application	Date of filing (day/month/year)
8.	Is a statement of inventorship and of right to grant of a patent required in support of this request? (Answer "Yes" if:	Yes	
	a) any applicant named in part 3 is not an inventor, or		
	b) there is an inventor who is not named as an applicant, or		
	c) any named applicant is a corporate body.		
	(see note (d))		

Patents Form 1/77

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Continuation sheets of this form

Description 27

Claim(s) 9

Abstract

Drawing(s)



10. If you are also filing any of the following, state how many against each item.

Priority documents

Translations of priority documents

Statement of inventorship and right to grant of a patent (Patents Form 7/77)

Request for preliminary examination and search (Patents Form 9/77)

One /

Request for substantive examination (Patents Form 10/77)

Any other documents (please specify)

11.

I/We request the grant of a patent on the basis of this application

Signature

Date

B. A. Yorke & Co

3. 6. 99

12. Name and daytime telephone number of person to contact in the United Kingdom

MRS E CHEETHAM - 0181 560 5847

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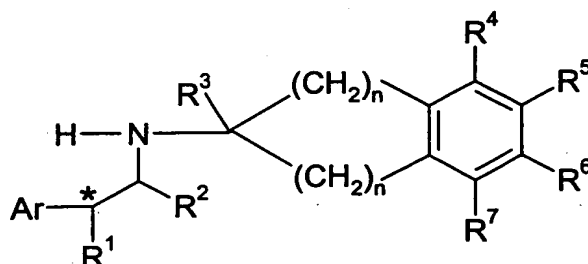
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Organic Compounds

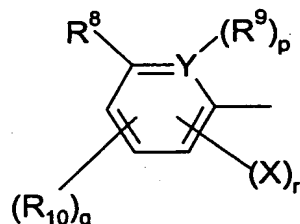
This invention relates to organic compounds, their preparation and their use as pharmaceuticals.

The invention provides in one aspect a compound of formula



in free or salt or solvate form, where

Ar is a group of formula



R¹ is hydrogen, hydroxy, or alkoxy,

R² and R³ are each independently hydrogen or alkyl,

R⁴, R⁵, R⁶ and R⁷ are each independently hydrogen, halogen, cyano, hydroxy, alkoxy, aryl, alkyl, alkyl interrupted by one or more hetero atoms, alkenyl, trialkylsilyl, carboxy, alkoxycarbonyl, or -CONR¹¹R¹² where R¹¹ and R¹² are each independently hydrogen or

alkyl, or R⁴ and R⁵, R⁵ and R⁶, or R⁶ and R⁷ together with the carbon atoms to which they are attached denote a carbocyclic or heterocyclic ring,

R⁸ is halogen, -OR¹³, -CH₂OR¹³ or -NHR¹³ where R¹³ is hydrogen, alkyl, alkyl interrupted by one or more hetero atoms, -COR¹⁴, where R¹⁴ is hydrogen, -N(R¹⁵)R¹⁶, alkyl or alkyl interrupted by one or more hetero atoms, or aryl and R¹⁵ and R¹⁶ are each independently hydrogen, alkyl or alkyl interrupted by one or more hetero atoms, or R¹³ is -C(=NH)R¹⁷, -SOR¹⁷ or -SO₂R¹⁷ where R¹⁷ is alkyl or alkyl interrupted by one or more hetero atoms, and

R^9 is hydrogen, or R^8 is $-NHR^{18}$ where $-NHR^{18}$ and R^9 , together with the carbon atoms to which they are attached, denote a 5- or 6- membered heterocycle,

R^{10} is $-OR^{19}$ or $-NHR^{19}$ where R^{19} is hydrogen, alkyl, alkyl interrupted by one or more hetero atoms, or $-COR^{20}$, where R^{20} is $-N(R^{21})R^{22}$, alkyl or alkyl interrupted by one or more hetero atoms, or aryl, and R^{21} and R^{22} are each independently hydrogen, alkyl or alkyl interrupted by one or more hetero atoms,

X is halogen or halomethyl or alkyl,

Y is carbon or nitrogen,

n is 1 or 2,

p is zero when Y is nitrogen or 1 when Y is carbon,

q and r are each zero or 1, the sum of q+r is 1 or 2; and

and the carbon atom marked with an asterisk* has the R or S configuration, or a mixture thereof, when R^1 is hydroxy or alkoxy.

Terms used in this specification have the following meanings:

"Alkyl" denotes straight chain or branched alkyl, which may be unsubstituted or substituted, for example by one or more halogen atoms or by one or more hydroxy or alkoxy groups, and which may be, for example, C_1 to C_{10} alkyl such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, straight or branched pentyl, straight or branched hexyl, straight or branched heptyl, straight or branched nonyl or straight or branched decyl, any of which may be unsubstituted or substituted by one or more halogen, preferably fluorine or chlorine, atoms, or by one or more C_1 to C_4 alkoxy groups. Preferably alkyl is C_1 to C_4 alkyl, especially unsubstituted C_1 to C_4 alkyl.

"Alkyl interrupted by one or more hetero atoms" denotes straight chain or branched alkyl e.g. C_2 to C_{10} alkyl, in which one or more pairs of carbon atoms are linked by $-O-$, $-NR-$, $-S-$, $-S(=O)-$ or $-SO_2-$, where R is hydrogen or C_1 to C_{10} (preferably C_1 to C_4) alkyl. Preferred such groups are alkoxyalkyl groups, preferably C_1 - C_4 -alkoxy- C_1 - C_4 -alkyl groups.

"Alkoxy" denotes straight chain or branched alkoxy and may be, for example, C_1 to C_{10} alkoxy such as methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy, sec-butoxy, tert-butoxy, or straight or branched pentoxy, hexyloxy, heptyloxy, octyloxy, nonyloxy or decyloxy. Preferably alkoxy is C_1 to C_4 alkoxy.

"Alkenyl" means straight chain or branched alkenyl, which may be unsubstituted or substituted, for example by one or more halogen atoms or one or more alkoxy groups, and which may be, for example, C₂ to C₁₀ alkenyl such as vinyl, 1-propenyl, 2-propenyl, 1-butenyl, isobutenyl, or straight or branched pentenyl, hexenyl, heptenyl, octenyl, nonenyl or decenyl. Preferred alkenyl is C₂ to C₄ alkenyl.

"Aryl" denotes unsubstituted or substituted aryl, e.g. unsubstituted phenyl or naphthyl, or phenyl or naphthyl substituted by one or more, e.g. 1 to 4, substituents selected from C₁-C₄-alkyl, hydroxy, C₁-C₄-alkoxy, halogen, or halo-C₁-C₄-alkyl. Preferably, aryl is unsubstituted phenyl or phenyl substituted by 1 or 2 substituents selected from C₁-C₄-alkyl or halogen.

The group Ar in formula II in which R⁸ is -NHR¹⁸ and -NHR¹⁸ and R⁹ together denote a 5- or 6- membered heterocycle may be, for example, a group in which Y is carbon, R⁸ is -NHR¹⁸ and -NHR¹⁸ and R⁹ together denote

a group of formula -NH-CO-R²³- where R²³ is an alkylene, alkenylene or alkyleneoxy group,
a group of formula -NH-SO₂-R²⁴ where R²⁴ is an alkyleneoxy group,
a group of formula -NH-R²⁵(COOR²⁶)- where R²⁵ is an alkylene or alkenylene group and R²⁶ is alkyl, or

a group of formula -NH-CO-NH- or -NH-CO-S-,

R¹⁰ is -OR¹⁹ where R¹⁹ is as hereinbefore defined,

X is alkyl,

p is 1, q is 1 and r is zero or 1.

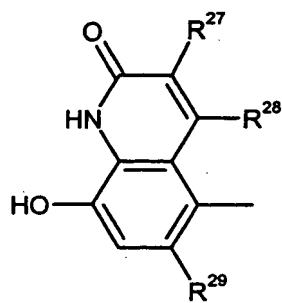
Preferred groups Ar of formula II in which R⁸ is -NHR¹⁸, and -NHR¹⁸ and R⁹ together denote a 5- or 6- membered heterocycle, include groups in which

Y is carbon, R⁸ is -NHR¹⁸ and -NHR¹⁸ and R⁹ together denote a group of formula
-NH-CO-C(R²⁷)=C(R²⁸)- or -NH-CO-CH₂-O- or -NH-CO-CH₂- or -NH-SO₂-CH₂-O- or -

~~NH-C(COOR²⁶)=CH- or -NH-CO-NH- or -NH-CO-S- where R²⁷ and R²⁸ are each~~
independently hydrogen or alkyl and R²⁶ is alkyl, R¹⁰ is -OH, X is alkyl, p is 1, q is 1 and r is zero or 1.

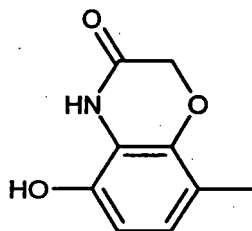
More preferred groups Ar of formula II where R⁸ is -NHR¹⁸, and -NHR¹⁸ and R⁹ together denote a 5- or 6- membered heterocycle include those of the formulae

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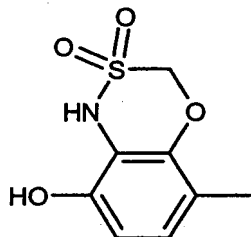


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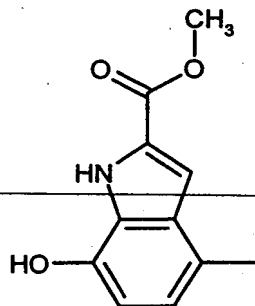
in which R^{27} , R^{28} and R^{29} are each independently hydrogen or C_1 - C_4 -alkyl.



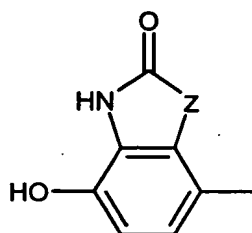
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V



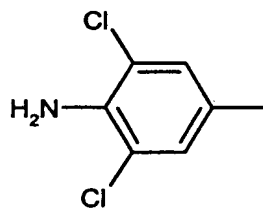
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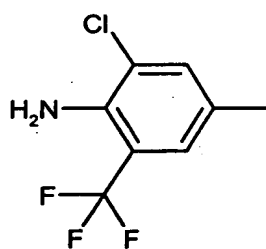
VII

in which Z is -O-, -NH- or -S-.

The group Ar of formula II in which R^8 is halogen and R^9 is hydrogen may be, for example, a group of formula II in which Y is carbon, R^8 is halogen, preferably chlorine, R^9 is hydrogen, R^{10} is $-NHR^{18}$ where R^{18} is hydrogen or C_1 - C_4 -alkyl, preferably hydrogen or methyl, X is halogen or halomethyl, preferably chlorine or trifluoromethyl, and p, q and r are each 1. Preferred groups Ar among such groups include those of formulae

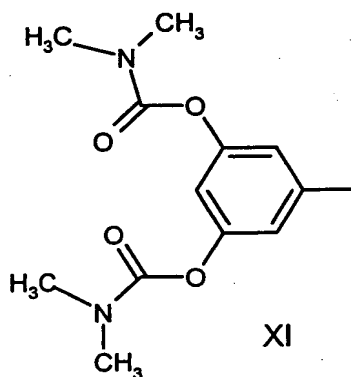
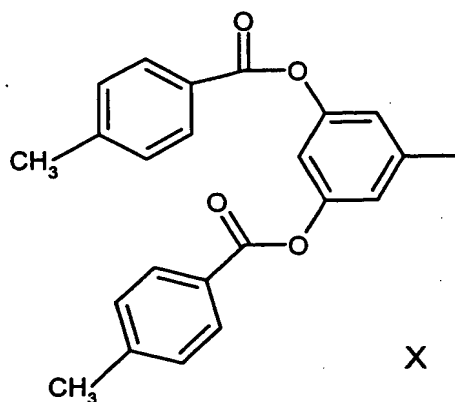


VIII

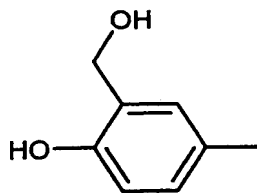


IX

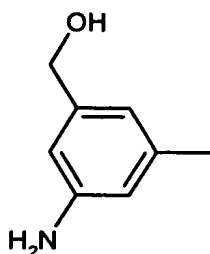
The group Ar of formula II in which R^8 is $-OR^{13}$ and R^9 is hydrogen may be, for example, a group of formula II in which Y is carbon, R^8 is $-OR^{13}$ where R^{13} is hydrogen, C_1 - C_4 -alkyl, C_1 - C_4 -alkoxy- C_1 - C_4 -alkyl, $-COR^{14}$ where R^{14} is C_1 - C_4 -alkyl, C_6 - C_{10} -aryl or $-N(R^{15})R^{16}$ where R^{15} and R^{16} are each independently hydrogen or C_1 - C_4 -alkyl, R^{10} is $-OR^{19}$ or $-NHR^{19}$ where R^{19} is hydrogen, C_1 - C_4 -alkyl, C_1 - C_4 -alkoxy- C_1 - C_4 -alkyl, or $-COR^{20}$ where R^{20} is $-N(R^{21})R^{22}$, C_1 - C_4 -alkyl, C_1 - C_4 -alkoxy- C_1 - C_4 -alkyl or C_6 - C_{10} -aryl and R^{21} and R^{22} are each independently hydrogen or C_1 - C_4 -alkyl, p and q are each 1 and r is zero. Preferred groups Ar among such groups include those of formulae



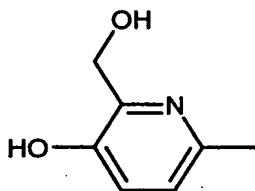
The group Ar of formula II in which R^8 is $-\text{CH}_2\text{OR}^{13}$ may be, for example, a group of formula II in which Y is carbon, R^8 is $-\text{CH}_2\text{OR}^{13}$ where R^{13} is hydrogen, $\text{C}_1\text{-C}_4\text{-alkyl}$, or $\text{C}_1\text{-C}_4\text{-alkoxy-C}_1\text{-C}_4\text{-alkyl}$, R^9 is hydrogen, R^{10} is $-\text{OR}^{19}$ where R^{19} is hydrogen, $\text{C}_1\text{-C}_4\text{-alkyl}$ or $\text{C}_1\text{-C}_4\text{-alkoxy-C}_1\text{-C}_4\text{-alkyl}$ or R^{10} is $-\text{NHR}^{19}$ where R^{19} is hydrogen, $\text{C}_1\text{-C}_4\text{-alkyl}$ or $-\text{COR}^{20}$ where R^{20} is $\text{C}_1\text{-C}_4\text{-alkyl}$, $\text{C}_6\text{-C}_{10}\text{-aryl}$ or $-\text{N}(\text{R}^{21})\text{R}^{22}$ where R^{21} and R^{22} are each independently hydrogen or $\text{C}_1\text{-C}_4\text{-alkyl}$, p and q are each 1 and r is zero; or a group of formula in which Y is nitrogen, R^8 is $-\text{CH}_2\text{OR}^{13}$ where R^{13} is hydrogen, $\text{C}_1\text{-C}_4\text{-alkyl}$ or $\text{C}_1\text{-C}_4\text{-alkoxy-C}_1\text{-C}_4\text{-alkyl}$, R^{10} is $-\text{OR}^{19}$ where R^{19} is hydrogen, $\text{C}_1\text{-C}_4\text{-alkyl}$ or $\text{C}_1\text{-C}_4\text{-alkoxy-C}_1\text{-C}_4\text{-alkyl}$, p and r are zero and q is 1. Preferred groups Ar among such groups include those of formulae



XII

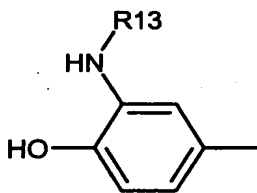


XIII



XIV

The group Ar of formula II in which R^8 is $-NHR^{13}$ may be, for example, a group of formula II in which Y is carbon, R^8 is $-NHR^{13}$ where R^{13} is hydrogen, C_1 - C_{10} alkyl, C_1 - C_{10} alkyl interrupted by 1 to 3 hetero atoms, $-COR^{14}$ where R^{14} is hydrogen, C_1 - C_{10} -alkyl or C_1 - C_{10} -alkyl interrupted by 1 to 3 hetero atoms, or R^{13} is $-C(=NH)R^{17}$, $-SOR^{17}$ or $-SO_2R^{17}$ where R^{17} is C_1 - C_{10} -alkyl or C_1 - C_{10} -alkyl interrupted by 1 to 3 hetero atoms, R^9 is hydrogen, R^{10} is $-OR^{18}$ where R^{18} is hydrogen, C_1 - C_4 -alkyl or C_1 - C_4 -alkoxy- C_1 - C_4 alkyl, p and q are each 1 and r is zero. Preferred groups Ar among such groups include those of formula



XV

Especially preferred groups Ar are those of formulae III, IV, V, XII and XV as hereinbefore defined.

The group R^1 in formula I may be, for example, hydrogen, hydroxy or C_1 - C_4 -alkoxy such as methoxy, ethoxy, isopropoxy, n-butoxy or tert-butoxy. Preferably, R^1 is hydroxy.

When R^1 is hydroxy or alkoxy, the carbon atom in formula I marked with an asterisk * preferably has the R configuration.

The groups R^2 and R^3 in formula I may be, for example, each independently hydrogen or C_1 - C_4 -alkyl, e.g. methyl or ethyl. Preferably R^2 and R^3 are each hydrogen.

The groups R^4 , R^5 , R^6 and R^7 in formula I may be, for example, each independently hydrogen, chlorine, fluorine, chloromethyl, trifluoromethyl, hydroxy, C_1 - C_{10} -alkoxy, C_1 - C_{10} -alkyl, C_1 - C_{10} -alkyl interrupted by one or more oxygen or sulfur atoms or one or more NH, SO or SO_2 groups, C_2 - C_4 -alkenyl, trimethylsilyl, triethylsilyl, phenyl, carboxy, C_1 - C_4 -alkoxycarbonyl, $-CONR^{11}R^{12}$ (where R^{11} and R^{12} are each independently hydrogen or C_1 - C_4 -alkyl), or R^4 and R^5 , R^5 and R^6 or R^6 and R^7 , together with the carbon atoms to which they are attached, may denote a 5- or 6- membered carbocyclic ring, which is preferably a cycloaliphatic ring which is preferably saturated, or a 5- or 6- membered O- heterocyclic ring containing one or two oxygen atoms. Preferably, R^4 , R^5 , R^6 and R^7 are each hydrogen or are such that the benzene ring to which they are attached is symmetrically substituted, i.e. either (a) R^4 and R^7 are identical and R^5 and R^6 are identical or together denote a symmetrical ring, or (b) R^4 and R^5 together and R^6 and R^7 together denote identical rings. More preferably, R^4 and R^7 are identical and are each hydrogen, C_1 - C_4 -alkyl or C_1 - C_4 -alkoxy, and either R^5 and R^6 are identical and are each hydrogen, C_1 - C_4 -alkyl, C_1 - C_4 -alkoxy or C_1 - C_4 -alkoxy- C_1 - C_4 -alkyl, or R^5 and R^6 together denote $-(CH_2)_s-$ or $-O(CH_2)_tO-$ where s is 3 or 4 and t is 1 or 2.

Especially preferred compounds of the invention include compounds of formula I in which Ar is a group of formula III, IV, V, XII or XV, R^1 is hydroxy, R^2 and R^3 are hydrogen, and R^4 and R^7 are identical and are each hydrogen, C_1 - C_4 -alkyl or C_1 - C_4 -alkoxy, and either R^5 and R^6 are identical and are each hydrogen, C_1 - C_4 -alkyl, C_1 - C_4 -alkoxy or C_1 - C_4 -alkoxy- C_1 - C_4 -alkyl, or R^5 and R^6 together denote $-(CH_2)_4-$ or $-O(CH_2)_2O-$, in free or salt or solvate form. In such compounds, the carbon atom in formula I marked with an asterisk * preferably has the R configuration. Specific especially preferred compounds are those described in the Examples hereinafter.

The compounds of formula (I) are capable of forming acid addition salts, particularly pharmaceutically acceptable acid addition salts. Pharmaceutically acceptable acid addition salts of the compound of formula I include those of inorganic acids, for example, hydrohalic acids such as hydrofluoric acid, hydrochloric acid, hydrobromic acid or hydroiodic acid, nitric acid, sulfuric acid, phosphoric acid; and organic acids such as formic acid, acetic acid, propionic acid, butyric acid, benzoic acid, o-hydroxybenzoic acid, p-hydroxybenzoic acid, p-chlorobenzoic acid, diphenylacetic acid, triphenylacetic acid, 1-hydroxynaphthalene-2-

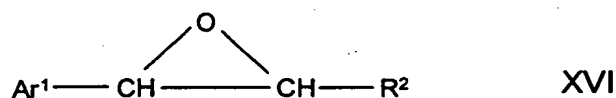
carboxylic acid, 3-hydroxynaphthalene-2-carboxylic acid, aliphatic hydroxy acids such as lactic acid, citric acid, tartaric acid or malic acid, dicarboxylic acids such as fumaric acid, maleic acid or succinic acid, and sulfonic acids such as methanesulfonic acid or benzenesulfonic acid. These salts may be prepared from compounds of formula I by known salt-forming procedures.

Suitable solvates are pharmaceutically acceptable solvates, preferably hydrates.

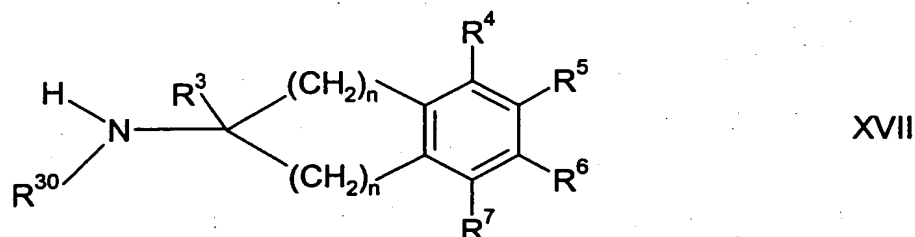
The present invention also provides a process for the preparation of compounds of formula I in free or salt or solvate form. They can be prepared by a process comprising:

(a) for the preparation of a compound where R^1 is hydroxy, either

(i) reacting a compound of formula

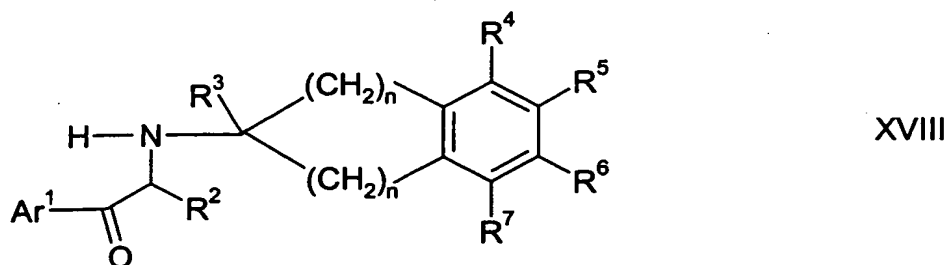


with a compound of formula



where Ar^1 is Ar as hereinbefore defined or a protected form thereof, R^2 , R^3 , R^4 , R^5 , R^6 , R^7 and n are as hereinbefore defined and R^{30} is hydrogen, or an amine-protective group, or

(ii) reducing a compound of formula



where Ar^1 , R^2 , R^3 , R^4 , R^5 , R^6 and R^7 are as hereinbefore defined, to convert the indicated keto group into $-\text{CH}(\text{OH})-$; or

(b) for the preparation of a compound where R^1 is hydrogen, reducing a corresponding compound of formula I where R^1 is hydroxy; or

(c) for the preparation of a compound of formula I where R^1 is alkoxy, O-alkylating a corresponding compound of formula I where R^1 is hydroxy;

and, optionally, converting a resultant compound of formula I in protected form into a corresponding compound in unprotected form;

and recovering the resultant compound of formula I in free or salt or solvate form.

Process variant (a)(i) may be carried out using known procedures for epoxide-amine reactions. It is conveniently carried out without a solvent or in an inert solvent, for example a hydrocarbon such as toluene. The reaction temperature is conveniently from 25°C to 200°C , preferably from 80°C to 150°C .

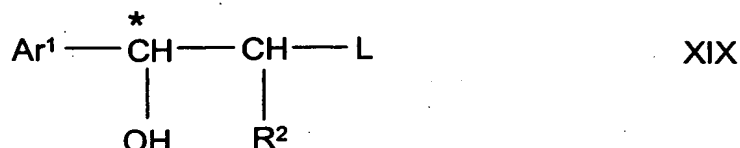
Process variant (a)(ii) may be carried out using conventional methods, for example by reaction with sodium borohydride under conventional conditions.

Process variant (b) may be carried out using known procedures for reduction of secondary alcohols to hydrocarbons. Process variant (c) may be carried out using known procedures for O-alkylation, for example by reaction with an alkylating agent such as an alkyl halide under known conditions.

Compounds of formula I in free form may be converted into salt or solvate forms, and vice versa, in a conventional manner.

Compounds of the invention can be recovered from the reaction mixture and purified in a conventional manner. Isomers, such as enantiomers, may be obtained in a conventional manner, e.g. by fractional crystallization or asymmetric synthesis from corresponding asymmetrically substituted, e.g. optically active, starting materials.

Compounds of formula XVI are known compounds or can be prepared by processes analogous to those used for the preparation of the known compounds, for example the procedures described in Journal of Medicinal Chemistry 1987, 30, 1563-1566. Compounds of formula XVI in which the carbon atom indicated by the asterisk * is chiral may be prepared from a compound of formula



where Ar^1 and R^2 are as hereinbefore defined and L is a leaving atom or group, as described in WO95/25104.

Compounds of formula XVI may alternatively be prepared by epoxidation of a compound of formula

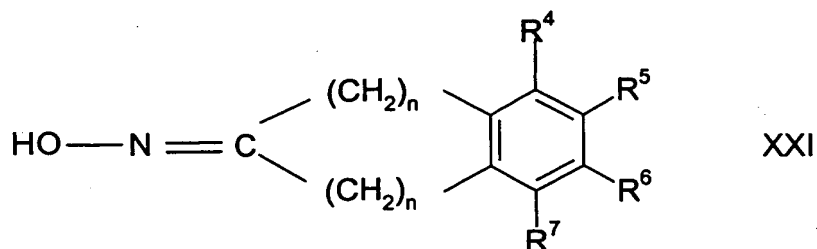


where Ar^1 and R^2 are as hereinbefore defined, using conventional procedures, such as those used in the Examples hereinafter.

Compounds of formula XX are known or may be prepared by methods analogous to those used for the preparation of known compounds, for example those used in the Examples hereinafter.

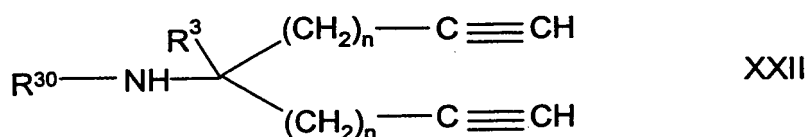
Compounds of formula XVII are known or may be prepared by methods analogous to those used for the preparation of the known compounds. R^{30} as an amine-protective group in formula XVII may be a known such group, for example as described in Protective Groups in Organic Synthesis, T.W.Greene, P.G.M. Wuts, John Wiley & Sons Inc, Second Edition, 1991, preferably benzyl or trifluoroacetyl.

For example, compounds of formula XVII, where R^3 is hydrogen, may be prepared by reducing an oxime of formula



where R^4 , R^5 , R^6 , R^7 and n are as hereinbefore defined. The reduction may be carried out by conventional methods for reducing oximes to amines. For example, the reduction may be carried out by catalytic hydrogenation, preferably using palladium on charcoal as the catalyst. The hydrogenation may be effected using known procedures, for example as described by R.D. Sindelar et al, J. Med. Chem. (1982), 25(7), 858-864. Oximes of formula XXI may be prepared as described by Sindelar et al, op.cit., or by analogous procedures.

Compounds of formula XVII where R^4 and R^7 are hydrogen can be prepared by reacting a compound of formula



with a compound of formula



where R^3 , R^5 , R^6 , R^{30} and n are as hereinbefore defined. The reaction may be carried out in the presence of a catalyst such as tris(triphenylphosphine)rhodium chloride. The reaction temperature may be, for example, from 60 to 120°C. The reaction is conveniently carried out in an inert solvent, for example ethanol, when the reaction temperature is conveniently about the reflux temperature of the solvent. The reaction may be carried out using known procedures, for example as described in WO96/23760. Where R^5 and R^6 are trialkylsilyl, the reaction between the compounds of formulae XXII and XXIII may be carried out in the presence of a metal carbonyl complex catalyst, for example using the procedure described by K.P.C. Vollhardt and R. Hillard, J. Am. Chem. Soc. 1977, 99(12), 4058, or an analogous procedure. Compounds of formula XXII may be prepared as described in WO96/23760 or by analogous procedures. Compounds of formula XXIII are known or may be prepared by known procedures.

Compounds of formula XVII as hereinbefore defined where R^4 , R^5 , R^6 and R^7 are such that the benzene ring to which they are attached is symmetrically substituted are novel, other than the compounds where R^4 , R^5 , R^6 , R^7 and R^{30} are each hydrogen, where R^4 and R^7 are methyl or methoxy when R^5 , R^6 and R^{30} are each hydrogen, and where R^4 , R^7 and R^{30} are hydrogen when R^5 and R^6 are each hydroxy, fluorine or chlorine. In particular, preferred intermediates of formula XVII are novel where (i) R^4 and R^7 are each hydrogen and R^5 and R^6 are either each C₂-C₄-alkyl, C₂-C₄-alkoxy, C₁-C₄-alkoxy-C₁-C₄-alkyl or R^5 and R^6 together denote $-(CH_2)_s-$ or $-O(CH_2)_tO-$ where s is 1 to 4 and t is 1 or 2; or (ii) R^4 and R^7 are each C₂-C₄-alkyl or C₂-C₄-alkoxy and R^5 and R^6 are either each hydrogen, C₁-C₄-alkyl, C₁-C₄-alkoxy and R^5 and R^6 are either each hydrogen, C₁-C₄-alkyl, C₁-C₄-alkoxy, or C₁-C₄-alkoxy-C₁-C₄-alkyl or R^5 and R^6 together denote $-(CH_2)_s-$ or $-O(CH_2)_tO-$ where s is 1 to 4 and t is 1 or 2.

Compounds of formula XVIII are novel compounds which may be prepared by reaction of a compound of formula



where Ar^1 is as hereinbefore defined and Hal is a halogen atom, preferably chlorine or bromine, with a compound of formula XVII as hereinbefore defined. The reaction may be carried out using conventional procedures, for example those described by Yoshizaki et al, J. Med. Chem (1976), 19(9), 1138-42.

Where desired, the protection of any reactive group may be carried out at any appropriate stage in the above processes. The protecting group is suitably one used conventionally in the art and may be introduced and removed using conventional procedure. For example, when a hydroxy group in Ar^1 is protected by a benzyl group, the latter may be removed by catalytic hydrogenation in the presence of palladium on charcoal using conventional procedures, such as those used hereinafter in the Examples.

Compounds of formula I in free, salt or solvate form are useful as pharmaceuticals. Accordingly the invention also provides a compound of formula I in free, salt or solvate form for use as a pharmaceutical. The compounds of formula I in free, salt or solvate form, hereinafter referred to alternatively as "agents of the invention", have good β_2 -adrenoreceptor agonist activity. The β_2 agonist activity, onset of action and duration of

action of the agents of the invention may be tested using the guinea pig tracheal strip in vitro assay according to the procedure of R.A. Coleman and A.T. Nials, J.Pharmacol. Methods (1989), 21(1), 71-86. The binding potency and selectivity for the β 2-adrenoreceptor relative to the β 1-adrenoreceptor can be measured by a classical filtration binding assay according to the procedure of Current Protocols in Pharmacology (S.J.Enna(editor-in-chief) et al, John Wiley & Son, Inc, 1998), or by cAMP determination in cells expressing β 2- or β 1-adrenoceptor, according to the procedure of B. January et al, British J. Pharmacol. 123: 701-711 (1998).

The agents of the invention have a rapid onset of action and have a prolonged stimulating action on the β 2-adrenoreceptor, compounds of the Examples hereinbelow having K_i (β 2) values of the order of 0.1 to 1000 nM, having durations of action of the order of 1 to greater than 12 hours, and having binding selectivities for the β 2-adrenoreceptor relative to the β 1-adrenoreceptor from 1.5 to 500.

Having regard to their β 2 agonist activity, the agents of the invention are indicated for use in the treatment of any condition which is prevented or alleviated by activation of the β 2-adrenoreceptor. In view of their long acting selective β 2 agonist activity, the agents of the invention are useful in the relaxation of bronchial smooth muscle and the relief of bronchoconstriction. The agents of the invention are therefore useful in the treatment of obstructive or inflammatory airways diseases. In view of their long duration of action, it is possible to administer the agents of the invention once-a-day in the treatment of such diseases.

Treatment of a disease in accordance with the invention may be symptomatic or prophylactic treatment. Inflammatory or obstructive airways diseases to which the present invention is applicable include asthma of whatever type or genesis including both intrinsic (non-allergic) asthma and extrinsic (allergic) asthma. Treatment of asthma is also to be understood as embracing treatment of subjects, e.g. of less than 4 or 5 years of age, exhibiting wheezing symptoms and diagnosed or diagnosable as "wheezy infants", an established patient category of major medical concern and now often identified as incipient or early-phase asthmatics. (For convenience this particular asthmatic condition is referred to as "wheezy-infant syndrome".)

Prophylactic efficacy in the treatment of asthma will be evidenced by reduced frequency or severity of symptomatic attack, e.g. of acute asthmatic or bronchoconstrictor attack, improvement in lung function or improved airways hyperreactivity. It may further be evidenced by reduced requirement for other, symptomatic therapy, i.e. therapy for or intended to restrict or abort symptomatic attack when it occurs, for example anti-inflammatory (e.g. corticosteroid) or bronchodilatory. Prophylactic benefit in asthma may in particular be apparent in subjects prone to "morning dipping". "Morning dipping" is a recognised asthmatic syndrome, common to a substantial percentage of asthmatics and characterised by asthma attack, e.g. between the hours of about 4 to 6 am, i.e. at a time normally substantially distant from any previously administered symptomatic asthma therapy.

Other inflammatory or obstructive airways diseases and conditions to which the present invention is applicable include adult respiratory distress syndrome (ARDS), chronic obstructive pulmonary or airways disease (COPD or COAD), including chronic bronchitis, or dyspnea associated therewith, emphysema, as well as exacerbation of airways hyperreactivity consequent to other drug therapy, in particular other inhaled drug therapy. The invention is also applicable to the treatment of bronchitis of whatever type or genesis including, e.g., acute, arachidic, catarrhal, croupus, chronic or phthinoïd bronchitis. Further inflammatory or obstructive airways diseases to which the present invention is applicable include pneumoconiosis (an inflammatory, commonly occupational, disease of the lungs, frequently accompanied by airways obstruction, whether chronic or acute, and occasioned by repeated inhalation of dusts) of whatever type or genesis, including, for example, aluminosis, anthracosis, asbestosis, chalicosis, ptilosis, siderosis, silicosis, tabacosis and byssinosis.

Having regard to their β_2 agonist activity, the agents of the invention are also useful in the treatment of a condition requiring relaxation of smooth muscle of the uterus or vascular system. They are thus useful for the prevention or alleviation of premature labour pains in pregnancy. They are also useful in the treatment of chronic and acute urticaria, psoriasis, allergic conjunctivitis, actinitis, hay fever, and mastocytosis.

The agents of the invention are also useful as co-therapeutic agents for use in conjunction with anti-inflammatory drug substances, particularly in the treatment of obstructive or

inflammatory airways diseases such as those mentioned hereinbefore, for example as potentiators of therapeutic activity of such drugs or as a means of reducing required dosaging or potential side effects of such drugs. An agent of the invention may be mixed with the anti-inflammatory drug in a fixed pharmaceutical composition or it may be administered separately, before, simultaneously with or after the anti-inflammatory drug. Such anti-inflammatory drugs include steroids, in particular glucocorticosteroids such as budesonide, beclamethasone, fluticasone or mometasone, and anticholinergic or antimuscarinic agents, in particular ipratropium bromide, oxitropium bromide and tiotropium bromide.

In accordance with the foregoing, the present invention also provides a method for the treatment of an obstructive or inflammatory airways disease which comprises administering to a subject, particularly a human subject, in need thereof a compound of formula I, or a pharmaceutically acceptable salt or solvate thereof, as hereinbefore described. In another aspect, the invention provides a compound of formula I, or a pharmaceutically acceptable salt or solvate thereof, as hereinbefore described for use in the preparation of a medicament for the treatment of an obstructive or inflammatory airways disease.

The agents of the invention may be administered by any appropriate route, e.g. orally, for example in the form of a tablet or capsule; parenterally, for example intravenously; topically to the skin, for example in the treatment of psoriasis; intranasally, for example in the treatment of hay fever; or, preferably, by inhalation, particularly in the treatment of obstructive or inflammatory airways diseases.

The invention thus also includes (A) a compound of formula I as hereinbefore described in free form, or a pharmaceutically acceptable salt or solvate thereof, in inhalable form; (B) an inhalable medicament comprising such a compound in inhalable form together with a pharmaceutically acceptable carrier in inhalable form; (C) a pharmaceutical product comprising such a compound in inhalable form in association with an inhalation device; and (D) an inhalation device containing such a compound in inhalable form.

Dosages employed in practising the invention will of course vary depending, for example, on the particular condition to be treated, the effect desired and the mode of administration. In general, suitable daily dosages for administration by inhalation are of the order of from 1 to 5000 μ g.

The invention is illustrated by the following Examples.

Compounds used in the Examples are prepared as follows:

Intermediate 1 - 5,6-Diethyl-inden-2-ylamine hydrochloride

Preparation 1 - 3-chloro-1-(3,4-diethylphenyl)- 1-propanone

1,2-Diethylbenzene (10.9 g, 74.6 mmol) and propionyl chloride (9.7 g, 74.6 mmol) are added dropwise to AlCl_3 (22.3 g, 167.8 mmol) in nitromethane (75 mL) over 30 min. The reaction mixture is stirred at room temperature for 2 hours, after which 70 g of ice and 14 mL concentrated sulphuric acid are added. The aqueous phase is extracted with ether, and the combined organic phases extracted with 2N HCl and saturated aqueous NaCl. The organic phase is further treated with activated charcoal, magnesium sulphate, and filtered, and the solvent removed *in vacuo*.

$^1\text{H-NMR}$ (CDCl_3) ppm: 7.8 (1H, s, Ar); 7.7 (1H, d, Ar); 7.2 (1H, d, Ar); 3.9 (2H, t, CH_2); 3.4 (2H, t, CH_2); 2.8 (4H, q, CH_2CH_3); 1.2 (6H, m, CH_3).

Preparation 2 - 2,3-dihydro-5,6-diethyl-1H-inden-1-one

3-chloro-1-(3,4-diethylphenyl)- 1-propanone (15.5 g) is dissolved in 66 mL concentrated sulphuric acid and heated to 90 °C for 4 hours. The reaction mixture is cooled, ice (70 g) is added, and the aqueous solution extracted twice with toluene. The organic layer is washed with sodium bicarbonate, saturated aqueous NaCl, and treated with activated charcoal and magnesium sulphate. After filtration, the solvent is removed *in vacuo*. The product is purified by flash column chromatography (silica, hexane / ethylacetate 10:1), and further crystallised in hexane.

$^1\text{H-NMR}$ (CDCl_3) ppm: 7.6 (1H, s, Ar); 7.3 (1H, d, Ar); 3.1 (2H, m, CH_2); 2.7 (6H, m, $\text{CH}_2+\text{CH}_2\text{CH}_3$); 1.2 (6H, m, CH_3).

Preparation 3 - 5,6-Diethyl- 3-oxime-1H-indene-1,2(3H)-dione

2,3-Dihydro-5,6-diethyl-1H-inden-1-one (5 g, 26 mmol) in methanol (75 mL) is brought to

40 °C, n-butyl nitrite (3.0 g, 28.6 mmol) is added dropwise, followed by the addition of concentrated HCl (1.25 mL). After 1 hour, the reaction is brought to room temperature and the precipitated product filtered off, washed with ice-cold methanol and dried.

¹H-NMR (d6-DMSO) ppm: 12.6 (1H, s, OH); 7.4 (1H, s, Ar); 7.3 (1H, d, Ar); 3.6 (2H, s, CH₂); 2.6 (4H, m, CH₂CH₃); 1.1 (6H, m, CH₃).

Preparation 4 - 5,6-Diethyl-indan-2-ylamine hydrochloride

5,6-Diethyl- 3-oxime-1H-indene-1,2(3H)-dione (4.5 g) is added to a mixture of acetic acid (150 mL), and concentrated sulphuric acid (4.5 mL). Pd/C 5% (1.5 g) is added, the reaction mixture degassed with nitrogen, and hydrogenated for 5 hours. The catalyst is then removed by filtration, the pH brought to pH 10 with 4M NaOH, and the solution extracted with chloroform. The organic phase is dried with magnesium sulphate, and the solvent removed *in vacuo*. The residue is redissolved in a minimum amount of ether, and HCl saturated ether added. The white precipitate is filtered and dried to yield the HCl salt of 5,6-diethyl-indan-2-ylamine, a compound of formula XVII where R³, R⁴ and R⁷ are H, R⁵ and R⁶ are each CH₃CH₂-, R³⁰ is hydrogen and n is 1.

¹H-NMR (d6-DMSO) ppm: 8.7 (3H, bd s, NH₃); 7.3 (2H, s, Ar); 4.2 (1H, bd s, CH); 3.5 (2H, dd, CH₂); 3.3 (2H, dd, CH₂); 2.8 (4H, q, CH₂CH₃); 1.4 (6H, t, CH₃).

Other compounds of formula XVII are prepared by procedures analogous to those used for Intermediate 1 or starting from available compounds and using procedures analogous to Preparations 3 and 4. These compounds of formula XVII are shown in the following table, R³ being hydrogen and n being 1 for all compounds.

Intermediate	R ⁴	R ⁵	R ⁶	R ⁷
2	CH ₃ CH ₂	H	H	CH ₃ CH ₂
3	H	-(CH ₂) ₄ -		H
4	H	-O(CH ₂) ₂ O-		H
5	H	CH ₃ (CH ₂) ₃	CH ₃ (CH ₂) ₃	H
6	H	CH ₃ (CH ₂) ₂	CH ₃ (CH ₂) ₂	H
7	H	CH ₃ O	CH ₃ O	H

Intermediate 2 : ES + MS m/e (MH⁺) : 204

Intermediate 3 : ¹H-NMR (d6-DMSO) ppm: 8.1 (3H, bd s, NH₃); 6.9 (2H, s, Ar); 3.9 (1H, bd s, CH); 3.2 (2H, dd, CH₂); 2.8 (2H, dd, CH₂); 2.7 (4H, m, CH₂Ar); 1.7 (6H, t, CH₂).

Intermediate 4 : ¹H-NMR (d6-DMSO) ppm: 8.3 (3H, bds, NH₃); 6.85 (2H, s, Ar); 4.2 (4H, s, 2CH₂); 3.1 (2H, dd, CH₂); 2.85 (2H, dd, CH₂).

Intermediate 5 : ¹H-NMR (d6-DMSO) ppm: 6.9 (2H, s, Ar); 3.8 (1H, m, CH); 3.1 (2H, dd, CH₂); 2.6 (2H, dd, CH₂); 2.5 (4H, t, 2CH₂); 1.65 (2H, bds, NH₂); 1.55 (4H, m, 2CH₂); 1.4 (4H, m, 2CH₂); 0.95 (6H, t, 2CH₃).

Intermediate 6 : ¹H-NMR (d6-DMSO) ppm: 8.1 (3H, bd s, NH₃); 7.0 (2H, s, Ar); 3.9 (1H, bd s, CH); 3.2 (2H, dd, CH₂); 2.8 (2H, dd, CH₂); 2.5 (4H, q, EtCH₂Ar); 1.6 (4H, q, CH₂), 0.9 (6H, t, CH₃).

Intermediate 7 : ¹H-NMR (d6-DMSO) ppm: 8.3 (3H, bd s, NH₃), 6.9 (2H, s, H-Ar), 3.9 (1H, bd m, CHN), 3.7 (6H, s, CH₃O), 3.2 (2H, dd, CH₂), 2.9 (2H, dd, CH₂).

Intermediate 8 - 2-(Trifluoroacetyl-amino)-5,6-bis(methoxymethyl)indane

According to the procedure of Magnus *et.al* (*Tetrahed. Lett.*, 34, 23-26 (1993)) a solution of commercially available 1,4-dimethoxy-2-butyne (1.32 g, 11.5 mmol) in nitrogen-degassed ethanol is heated to 80°C with stirring under a nitrogen atmosphere.

Tris(triphenylphosphine)rhodium chloride (64 mg, 0.07 mmol) and a solution of 2,2,2-trifluoro-N-[1-(2-propynyl)-3-butyryl]-acetamide (470 mg, 2.32 mmol; prepared from literature procedure: Romero, Arthur G.; Leiby, Jeffrey A PCT Int. Appl. WO 9623760) in nitrogen-degassed ethanol (2 ml) are added in portions over 2 hours. The mixture is stirred under nitrogen at 80°C for a further 3 hours. ~~The solvent is removed under vacuo and the~~ residue is purified by flash chromatography on silica gel, eluting with hexane/ethyl acetate (2:1)

¹H-NMR (CDCl₃) ppm: 2.9 (2H, dd), 3.35 (2H, dd), 3.45 (6H, s), 4.57 (4H, s), 4.85 (1H, m), 6.4 (1H, br s), 7.30 (2H, s).

Intermediate 9 - 2-Amino-5,6-bis(methoxymethyl)indane

A solution of potassium hydroxide (150 mg, 2.60 mmol) in water (0.5 ml) is added to a solution of 2-(trifluoroacetyl-amino)-5,6-bis(methoxymethyl)indane (240 mg, 0.75 mmol) in methanol (3 mL) and the mixture is heated at reflux for 2.5 hours. The solvent was removed *in vacuo* and the residue is partitioned between aqueous sodium hydroxide (10 mL) and ethyl acetate (20 mL). The organic extract is dried (MgSO₄) and the solvent is removed *in vacuo* to leave the product as a dark oil.

¹H-NMR (CDCl₃) ppm: 2.60 (2H, dd), 3.10 (2H, dd), 3.33 (6H, s), 3.75 (1H, m), 4.42 (4H, s), 7.17 (2H, s).

Intermediate 10 - 8-Hydroxy-5-[(indan-2-ylamino)-acetyl]-1.H.-quinolin-2-one

5-(Chloroacetyl)-8-hydroxy-2(1H)-quinolinone (25 mg, 0.105 mmol) prepared from literature procedure (Yoshizaki, Shiro; Tanimura, Kaoru; Tamada, Shigeharu; Yabuuchi, Youichi; Nakagawa, Kazuyuki. J. Med. Chem. (1976), 19(9), 1138-42) is reacted neat with indan-2-ylamine (205 mg, 1.21 mmol) at 25 °C for 2 hours. The reaction mixture is purified by flash chromatography (silica, CH₂Cl₂/ methanol 9:1)

ES+ MS *m/e* 335 (MH⁺).

Intermediate 11

This compound of formula XVIII where Ar is a group of formula III, R²⁷, R²⁸ and R²⁹ are hydrogen, R², R³, R⁴ and R⁷ are hydrogen, and R⁵ and R⁶ are each methoxy, is prepared by a procedure analogous to that used for preparation of Intermediate 10. ES+MS *m/e*(MH⁺):395.

Intermediate 12 - 8-Benzoyloxy-3-methyl-5-oxiranyl-1.H.-quinolin-2-one8-Hydroxy-3-methyl-1.H.-quinolin-2-one

This is prepared according to the procedure of Wang *et al* (T.-C. Wang, Y.-L. Chen, K.-H. Lee, C.-C. Izeng *Synthesis* 1997, 87-90.).

$^1\text{H-NMR}$ ($\text{d}_4\text{-CH}_3\text{OH}$) ppm: 2.14 (s, 3H), 6.84-6.89 (m, 1H), 6.95-7.03 (m, 2H), 6.90 (s, 1H), 7.71 (s, 1H).

8-Benzyloxy-3-methyl-1.H.-quinolin-2-one

Benzyl bromide (1.28 mL) is added to a suspension of potassium carbonate (2.98 g) in a solution of 8-hydroxy-3-methyl-1.H.-quinolin-2-one (1.26 g) in acetone (36 mL) at room temperature. The reaction mixture is refluxed for 18 hours, filtered, evaporated and purified by flash column chromatography on silica gel, eluting with 2% methanol in dichloromethane.

$^1\text{H-NMR}$ (CDCl_3) ppm: 2.11 (s, 3H), 5.13 (s, 2H), 6.92-6.98 (m, 1H), 7.02-7.08 (m, 2H), 7.29-7.40 (m, 5H), 7.57 (s, 1H), 9.23 (s, 1H).

8-Benzyloxy-5-bromo-3-methyl-1.H.-quinolin-2-one

A solution of bromine (0.57 g) in acetic acid (2 mL) is added dropwise to a solution of 8-benzyloxy-3-methyl-1.H.-quinolin-2-one (0.94g) and sodium acetate (0.96 g) in acetic acid (12 mL) at room temperature. The reaction mixture is stirred at room temperature for 3 hours, evaporated, the residue partitioned between water (5 mL) and ethyl acetate (5 mL), extracting a further 2x with ethyl acetate (5 mL). Combined organic extracts are dried over magnesium sulphate and purified by flash column chromatography on silica gel, eluting with 2% methanol in dichloromethane.

$^1\text{H-NMR}$ (CDCl_3) ppm: 2.27 (s, 3H), 5.18 (s, 2H), 6.83 (d, 1H), 7.39 (d, 1H), 7.37-7.41 (m, 5H), 7.91 (s, 1H), 9.08 (s, 1H).

8-Benzyloxy-3-methyl-5-vinyl-1.H.-quinolin-2-one

Palladium terakis(triphenylphosphine) (30 mg) is added to a solution of 8-benzyloxy-5-bromo-3-methyl-1.H.-quinolin-2-one (239 mg) and tributylvinyltin (203 μL) in toluene (7 mL) at room temperature. The reaction mixture is heated for 2 hours at 100 $^\circ\text{C}$, cooled to room temperature, evaporated and the product purified by flash column chromatography on silica gel, eluting with 2% ethyl acetate in dichloromethane.

¹H-NMR (CDCl₃) ppm: 2.24 (s, 3H), 5.18 (s, 2H), 5.32-5.39 (m, 1H), 5.61-5.68 (m, 1H), 6.95 (d, 1H), 7.09-7.20 (m, 1H), 7.21-7.26 (m, 2H), 7.31-7.43 (m, 4H), 7.89 (s, 1H), 9.20 (s, 1H).

8-Benzyloxy-3-methyl-5-oxiranyl-1.H.-quinolin-2-one

To 8-benzyloxy-3-methyl-5-vinyl-1.H.-quinolin-2-one (300 mg) is added to a 0.1M solution of dimethyldioxirane in acetone (12.4 mL). After stirring at room temperature for 2 hours, the solvent is removed *in vacuo* to yield the product.

¹H-NMR (CDCl₃) ppm: 2.23 (s, 3H), 2.77-2.81 (m, 1H), 3.18-3.23 (m, 1H), 4.17-4.21 (m, 1H), 5.18 (s, 2H), 6.91 (d, 1H), 7.01 (d, 1H), 7.93 (s, 1H), 9.10 (s, 1H).

Intermediate 13 - 8-Benzyloxy-5-[2-(5,6-diethyl-indan-2-ylamino)-1-hydroxy-ethyl]-3-methyl-1.H.-quinolin-2-one

A solution of Intermediate 12 (65 mg) and 5,6-diethyl-indan-2-ylamine (120 mg) in DMSO (1.5 mL) is heated for 18 hours at 90 °C. The solvent is removed *in vacuo*, and the product purified by flash chromatography on silica gel, eluting with 10% methanol in dichloromethane.

¹³C-NMR (d₄-CH₃OH) ppm: 15.96, 17.14, 26.33, 36.77, 53.34, 59.82, 67.33, 71.73, 112.09, 118.98, 121.73, 125.42, 128.74, 129.24, 129.47, 129.61, 131.84, 134.56, 137.52, 137.64, 142.29, 145.94, 164.02.

Intermediate 14 - 8-Methoxymethoxy-6-methyl-5-oxiranyl-1.H.-quinolin-2-one

8-Hydroxy-6-methyl-1.H.-quinolin-2-one

This is prepared according to the procedure of Wang *et al* (T.-C. Wang, Y.-L. Chen, K.-H. Lee, C.-C. Izeng *Synthesis* 1997, 87-90.).

¹H-NMR (d₆-DMSO) ppm: 2.26 (s, 3H), 6.45 (d, 1H), 6.79 (s, 1H), 6.90 (s, 1H), 7.78 (d, 1H).

5-Bromo-8-hydroxy-6-methyl-1.H.-quinolin-2-one

A 45% solution of hydrobromic acid in acetic acid (324 μ L) is added dropwise to a solution of 8-hydroxy-6-methyl-1.H.-quinolin-2-one (316 mg) in dimethylsulphoxide (9 mL) at room temperature. The reaction mixture is allowed to stand for 18 hours at room temperature and the solvent removed *in vacuo*.

$^1\text{H-NMR}$ (d_6 -DMSO) ppm: 2.33 (s, 3H), 6.58 (d, 1H), 6.92 (s, 1H), 8.03 (d, 1H), 10.44 (s, 1H), 10.67 (s, br, 1H).

5-Bromo-8-methoxymethoxy-6-methyl-1.H.-quinolin-2-one

Methoxymethyl chloride (410 μ L) was added to a suspension of potassium carbonate (1.24 g) in a solution of 5-bromo-8-hydroxy-6-methyl-1.H.-quinolin-2-one (480 mg) in dimethylformamide (9 mL) at 0 $^\circ\text{C}$. The reaction mixture is stirred for 18 hours at room temperature, filtered, the solvent removed *in vacuo*, and the product purified by flash column chromatography on silica gel, eluting with 2% methanol in dichloromethane.

$^{13}\text{C-NMR}$ (CDCl_3) ppm: 23.42, 56.52, 95.07, 115.78, 116.19, 119.32, 123.30, 128.13, 132.14, 139.78, 141.78, 161.32.

8-Methoxymethoxy-6-methyl-5-vinyl-1.H.-quinolin-2-one

Bis-(triphenylphosphine)palladium (II) chloride (98 mg) is added to a solution of 5-bromo-8-methoxymethoxy-6-methyl-1.H.-quinolin-2-one (410 mg) and tributylvinyltin (603 μ L) in dimethylformamide (14 mL) at room temperature. The reaction mixture is heated for 24 hours at 90 $^\circ\text{C}$, evaporated and purified by flash column chromatography on silica gel, eluting with 2% methanol in dichloromethane.

$^1\text{H-NMR}$ (CDCl_3) ppm: 2.19 (s, 3H), 3.41 (s, 3H), 5.18 (d, 1H), 5.20 (s, 2H), 5.60 (d, 1H), 6.52 (d, 1H), 6.63-6.69 (m, 1H), 6.96 (s, 1H), 7.95 (d, 1H), 9.78 (s, 1H).

8-Methoxymethoxy-6-methyl-5-oxiranyl-1.H.-quinolin-2-one

This is obtained from 8-methoxymethoxy-6-methyl-5-vinyl-1H-quinolin-2-one (186 mg) according to the last step of the procedure for Intermediate 12.

¹H-NMR (CDCl₃) ppm: 2.38 (s, 3H), 2.68-2.72 (m, 1H), 3.19-3.23 (m, 1H), 3.43 (s, 3H), 3.97-4.01 (m, 1H), 5.21 (s, 2H), 6.60 (d, 1H), 6.98 (s, 1H), 8.22 (d, 1H), 9.09 (s, 1H).

Intermediate 15, (R)-2-(4-benzyloxy-3-nitrophenyl)-oxirane, is prepared according to the procedure of R. Hett et al, Tetrahedron Lett. (1997), 38(7), 1125-1128.

Example 1

(R)-8-Benzyloxy-5-[2-(4,7-dimethoxy-indan-2-ylamino)-1-hydroxy-ethyl]-1H-quinolin-2-one

(R)-8-Benzyloxy-5-oxiranylcabostyryl (100mg, 0.34mmol), prepared from literature procedure (Beeley, Lee James; Dean, David Kenneth, PCT Int. Appl. WO 9525104) and 4,7-dimethoxy-indan-2-ylamine (66mg, 0.34mmol), prepared from literature procedure (Sindelar, R. D.; Mott, J.; Barfknecht, C. F.; Arneric, S. P.; Flynn, J. R.; Long, J. P.; Bhatnagar, R. K. J. Med. Chem. (1982), 25(7), 858-64), are dissolved in toluene (1mL). The reaction mixture was heated to 110°C and the solvent is allowed to evaporate. The residue is then stirred at 110°C for 4 hours. The reaction is shown to be complete by TLC. The product is purified by flash column chromatography (silica, dichloromethane / methanol 20:1).

TLC (silica, dichloromethane / methanol 25:1 R_f = 0.10).
ES+ MS *m/e* 487 (MH⁺).

(R)-5-[2-(4,7-Dimethoxy-indan-2-ylamino)-1-hydroxy-ethyl]-1H-quinolin-2-one
hydrochloride

(R)-8-Benzyloxy-5-[2-(4,7-dimethoxy-indan-2-ylamino)-1-hydroxy-ethyl]-1H-quinolin-2-one (37mg, 0.08mmol) is dissolved in methanol (10mL) and the compound is deprotected by adding a catalytic amount of 10% palladium on charcoal and placing the solution under an atmosphere of hydrogen. The reaction is shown to be complete by TLC after 4 hours. The catalyst is filtered off, 1M HCl/Et₂O (1.1 equivalent) is added and the solvent is removed *in vacuo*.

TLC (silica, dichloromethane / methanol 10:1 R_f = 0.15).

ES+ MS m/e 397 (MH^+).

Other compounds of formula I are prepared from (R)-8-benzyloxy-5-oxiranylcarbostyryl ((R)-2-(4-benzyloxy-3-nitrophenyl)-oxirane (Intermediate 15) in Example 11) and the appropriate compound of formula XVII by procedures analogous to Example 1. These compounds, in which R^1 is OH, R^2 and R^3 are H, Ar is a group of formula III in which R^{27} , R^{28} and R^{29} are H (except in Example 11, where Ar is a group of formula XV in which R^{13} is H) and n is 1 (except in Example 9 where n is 2) are shown in the following table.

Example	R^4	R^5	R^6	R^7	ES+MS m/e (MH^+)
2	H	CH_3CH_2	CH_3CH_2	H	393
3	H	CH_3	CH_3	H	365
4	CH_3CH_2	H	H	CH_3CH_2	393
5	H	$-(CH_2)_4-$		H	391
6	H	$-O(CH_2)_2O-$		H	395
7	H	$CH_3(CH_2)_3$	$CH_3(CH_2)_3$	H	449
8	H	$CH_3(CH_2)_2$	$CH_3(CH_2)_2$	H	421
9	H	H	H	H	365
10	H	CH_3OCH_2	CH_3OCH_2	H	
11	H	CH_3CH_2	CH_3CH_2	H	341

Example 10: 1H -NMR (d_4 -MeOH) ppm: 2.78 (2H, m), 2.9 (2H, m), 3.15 (2H, m), 3.28 (6H, s), 3.7 (1H, m), 4.55 (1H, br s), 5.15 (1H, m), 6.58 (1H, d), 6.9 (1H, d), 7.11 (2H, s), 7.15 (1H, s), 8.25 (1H, s).

Example 12

8-Hydroxy-5-[1-hydroxy-2-(indan-2-ylamino)-ethyl]-1H-quinolin-2-one

Intermediate 10 (18 mg, 0.054 mmol) is dissolved in methanol (2 mL) and cooled on ice. Sodium borohydride (6 mg, 0.12 mmol) is added over 2 hours. Concentrated HCl is then added until pH reaches 1, and the reaction mixture filtered. The filtrate is washed with methanol. The combined liquid phases are evaporated and redissolved in methanol twice.

After removal of the methanol in vacuo, the residue is redissolved in water and the pH brought to 12 with 1N KOH. The solvent is removed in vacuo and the residue coevaporated twice with toluene. The residue is purified by flash chromatography (silica, CH₂Cl₂/methanol 8:2).

ES+ MS *m/e* 337 (MH⁺).

Example 13

5-[2-(5,6-Dimethoxy-indan-2-ylamino)-1-hydroxy-ethyl]-8-hydroxy-1.H.-quinolin-2-one

This compound is prepared from Intermediate 11 by a procedure analogous to that of Example 12.

ES+MS *m/e* 397 (MH⁺)

Example 14

5-[2-(5,6-Diethyl-indan-2-ylamino)-1-hydroxy-ethyl]-8-hydroxy-3-methyl-1.H.-quinolin-2-one

This is prepared from Intermediate 13 (21mg) by the hydrogenation procedure for removal of the benzyl group used in Example 1.

¹H-NMR (d₄-CH₃OH) ppm 1.11 (t, 6H), 2.11 (s, 3H), 2.58 (q, 4H), 3.01-3.37 (m, 6H), 4.10-4.16 (m, 1H), 5.31-5.38 (m, 1H), 6.91 (d, 1H), 7.00 (s, 2H), 7.21 (d, 1H), 8.13 (s, 1H).

Example 15

5-[2-(5,6-Diethyl-indan-2-ylamino)-1-hydroxy-ethyl]-8-methoxymethoxy-6-methyl-1.H.-quinolin-2-one

This is obtained from Intermediate 14 (20 mg) and 5,6-diethyl-indan-2-ylamine (72 mg) according to the procedure used for preparation of Intermediate 13.

¹H-NMR (CDCl₃) ppm: 1.14 (t, 6H), 2.30 (s, 3H), 2.51 (q, 4H), 2.64-3.16 (m, 6H), 3.41 (s, 3H), 3.60-3.68 (m, 1H), 5.18-5.25 (m, 3H), 6.50 (d, 1H), 7.89-7.94 (m, 3H), 8.68 (d, 2H), 9.15 (s, br, 1H).

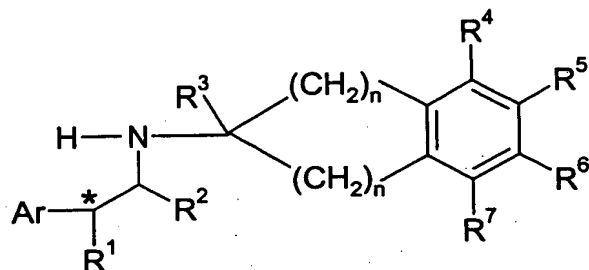
5-[2-(5,6-Diethyl-indan-2-ylamino)-1-hydroxy-ethyl]-8-hydroxy-6-methyl-1.H.-quinolin-2-one

3N Hydrochloric acid (1mL) is added to a solution of 5-[2-(5,6-Diethyl-indan-2-ylamino)-1-hydroxy-ethyl]-8-methoxymethoxy-6-methyl-1.H.-quinolin-2-one (12 mg) in isopropanol (1mL) and tetrahydrofuran (1mL) at room temperature and the reaction mixture heated for 18 hours at 40°C. The solvent is removed *in vacuo*, and the product purified by preparative scale HPLC on a C8 column, eluting with a water/acetonitrile/trifluoroacetic acid gradient.

¹³C-NMR (d₄-CH₃OH) ppm: 15.97, 20.09, 26.34, 36.87, 51.75, 59.72, 67.33, 118.41, 119.12, 121.21, 125.45, 126.11, 128.60, 133.35, 137.52, 137.55, 142.32, 142.50, 145.69, 163.24.

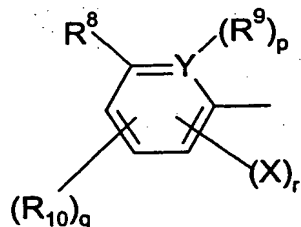
Claims

1. A compound of formula



in free or salt or solvate form, where

Ar is a group of formula



R^1 is hydrogen, hydroxy, or alkoxy,

R^2 and R^3 are each independently hydrogen or alkyl,

R^4 , R^5 , R^6 and R^7 are each independently hydrogen, halogen, cyano, hydroxy, alkoxy, aryl, alkyl, alkyl interrupted by one or more hetero atoms, alkenyl, trialkylsilyl, carboxy, alkoxy carbonyl, or $-\text{CONR}^{11}\text{R}^{12}$, where R^{11} and R^{12} are each independently hydrogen or alkyl, or R^4 and R^5 , R^5 and R^6 , or R^6 and R^7 together with the carbon atoms to which they are attached denote a carbocyclic or heterocyclic ring,

R^8 is halogen, $-\text{OR}^{13}$, $-\text{CH}_2\text{OR}^{13}$ or $-\text{NHR}^{13}$ where R^{13} is hydrogen, alkyl, alkyl interrupted by one or more hetero atoms, $-\text{COR}^{14}$, where R^{14} is hydrogen, $-\text{N}(\text{R}^{15})\text{R}^{16}$, alkyl or alkyl

interrupted by one or more hetero atoms, or aryl and R^{15} and R^{16} are each independently hydrogen, alkyl or alkyl interrupted by one or more hetero atoms, or R^{13} is $-\text{C}(=\text{NH})\text{R}^{17}$, $-\text{SOR}^{17}$ or $-\text{SO}_2\text{R}^{17}$ where R^{17} is alkyl or alkyl interrupted by one or more hetero atoms, and R^9 is hydrogen, or R^8 is $-\text{NHR}^{18}$ where $-\text{NHR}^{18}$ and R^9 , together with the carbon atoms to which they are attached, denote a 5- or 6- membered heterocycle,

R^{10} is $-\text{OR}^{19}$ or $-\text{NHR}^{19}$ where R^{19} is hydrogen, alkyl, alkyl interrupted by one or more hetero atoms, or $-\text{COR}^{20}$, where R^{20} is $-\text{N}(\text{R}^{21})\text{R}^{22}$, alkyl or alkyl interrupted by one or more

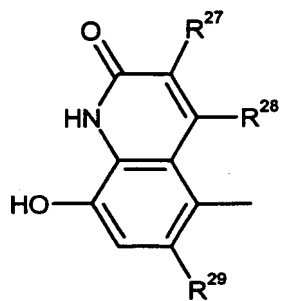
hetero atoms, or aryl, and R^{21} and R^{22} are each independently hydrogen, alkyl or alkyl interrupted by one or more hetero atoms,
 X is halogen or halomethyl or alkyl,
 Y is carbon or nitrogen,
 n is 1 or 2,
 p is zero when Y is nitrogen or 1 when Y is carbon,
 q and r are each zero or 1, the sum of q+r is 1 or 2; and
 and the carbon atom marked with an asterisk* has the R or S configuration, or a mixture thereof, when R^1 is hydroxy or alkoxy.

2. A compound according to claim 1, in which Ar is a group of formula II in which
 Y is carbon,
 R^8 is $-NHR^{18}$ and $-NHR^{18}$ and R^9 together denote
 a group of formula $-NH-CO-R^{23}$ - where R^{23} is an alkylene, alkenylene or alkyleneoxy group,
 a group of formula $-NH-SO_2-R^{24}$ where R^{24} is an alkyleneoxy group,
 a group of formula $-NH-R^{25} (COOR^{26})$ - where R^{25} is an alkylene or alkenylene group and
 R^{26} is alkyl, or
 a group of formula $-NH-CO-NH-$ or $-NH-CO-S-$,
 R^{10} is $-OR^{19}$, where R^{19} is as defined in claim 1,
 X is alkyl,
 p is 1, q is 1 and r is zero or 1.

3. A compound according to claim 2, in which $-NHR^{18}$ and R^9 together denote a group of
 formula $-NH-CO-C(R^{27})=C(R^{28})-$, $-NH-CO-CH_2-O-$, $-NH-CO-CH_2-$, $-NH-SO_2-CH_2-O-$, $-NH-C(COOR^{26})=CH-$, $-NH-CO-NH-$, or $-NH-CO-S-$, where R^{27} and R^{28} are each
 independently hydrogen or alkyl and R^{26} is alkyl, R^{10} is $-OH$, X is alkyl, p is 1, q is 1 and r is
 zero or 1.

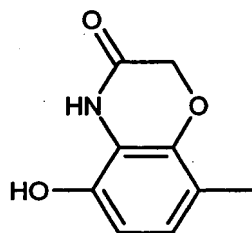
4. A compound according to claim 3, in which Ar is a group of formula III, IV, V, VI or VII

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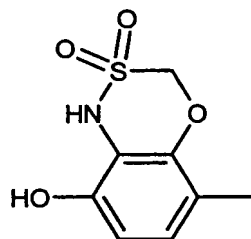


III

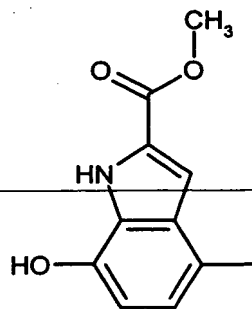
in which R^{27} , R^{28} and R^{29} are each independently hydrogen or C_1 - C_4 -alkyl



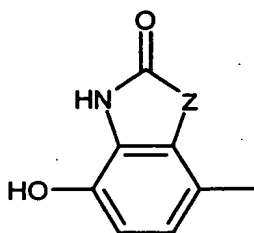
IV



V



VI

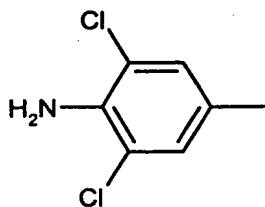


VII

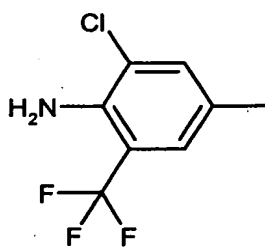
in which Z is -O-, -NH- or -S-.

5. A compound according to claim 1, in which Y is carbon, R^8 is halogen, R^9 is hydrogen, R^{10} is $-NHR^{18}$ where R^{18} is hydrogen or C_1 - C_4 -alkyl, X is halogen or halomethyl, and p, q and r are each 1.

6. A compound according to claim 5, in which Ar is a group of formula VIII or IX



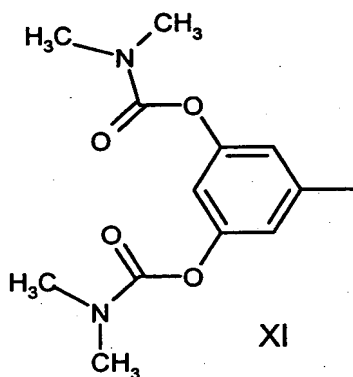
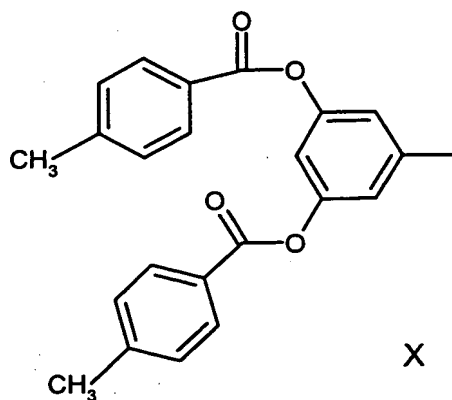
VIII



IX

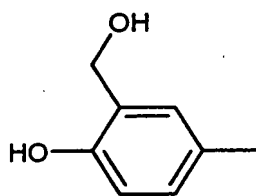
7. A compound according to claim 1, in which Ar is a group of formula II in which Y is carbon, R^8 is $-OR^{13}$ where R^{13} is hydrogen, C_1 - C_4 -alkyl, C_1 - C_4 -alkoxy- C_1 - C_4 -alkyl, $-COR^{14}$ where R^{14} is C_1 - C_4 -alkyl, C_6 - C_{10} -aryl or $-N(R^{15})R^{16}$ where R^{15} and R^{16} are each independently hydrogen or C_1 - C_4 -alkyl, R^{10} is $-OR^{19}$ or $-NHR^{19}$ where R^{19} is hydrogen, C_1 - C_4 -alkyl, C_1 - C_4 -alkoxy- C_1 - C_4 -alkyl, or $-COR^{20}$ where R^{20} is $-N(R^{21})R^{22}$, C_1 - C_4 -alkyl, C_1 - C_4 -alkoxy- C_1 - C_4 -alkyl or C_6 - C_{10} -aryl and R^{21} and R^{22} are each independently hydrogen or C_1 - C_4 -alkyl, p and q are each 1 and r is zero.

8. A compound according to claim 7, in which Ar is a group of formula X or XI

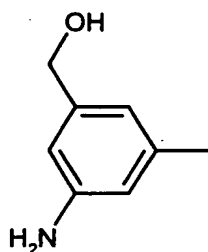


9. A compound according to claim 1, in which Ar is a group of formula II in which Y is carbon, R^8 is $-\text{CH}_2\text{OR}^{13}$ where R^{13} is hydrogen, $\text{C}_1\text{-C}_4\text{-alkyl}$, or $\text{C}_1\text{-C}_4\text{-alkoxy-C}_1\text{-C}_4\text{-alkyl}$, R^9 is hydrogen, R^{10} is $-\text{OR}^{19}$ where R^{19} is hydrogen, $\text{C}_1\text{-C}_4\text{-alkyl}$ or $\text{C}_1\text{-C}_4\text{-alkoxy-C}_1\text{-C}_4\text{-alkyl}$ or R^{10} is $-\text{NHR}^{19}$ where R^{19} is hydrogen, $\text{C}_1\text{-C}_4\text{-alkyl}$ or $-\text{COR}^{20}$ where R^{20} is $\text{C}_1\text{-C}_4\text{-alkyl}$, $\text{C}_6\text{-C}_{10}\text{-aryl}$ or $-\text{N(R}^{21})\text{R}^{22}$ where R^{21} and R^{22} are each independently hydrogen or $\text{C}_1\text{-C}_4\text{-alkyl}$, p and q are each 1 and r is zero; or a group of formula II in which Y is nitrogen, R^8 is $-\text{CH}_2\text{OR}^{13}$ where R^{13} is hydrogen, $\text{C}_1\text{-C}_4\text{-alkyl}$ or $\text{C}_1\text{-C}_4\text{-alkoxy-C}_1\text{-C}_4\text{-alkyl}$, R^{10} is $-\text{OR}^{19}$ where R^{19} is hydrogen, $\text{C}_1\text{-C}_4\text{-alkyl}$ or $\text{C}_1\text{-C}_4\text{-alkoxy-C}_1\text{-C}_4\text{-alkyl}$, p and r are zero and q is 1.

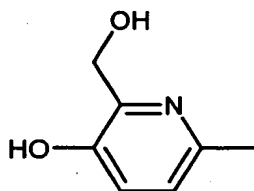
10. A compound according to claim 9, in which Ar is a group of formula XII, XIII or XIV



XII



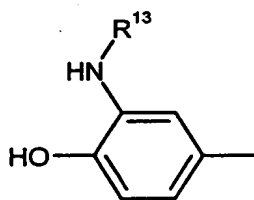
XIII



XIV

11. A compound according to claim 1, in which Ar is a group of formula II in which Y is carbon, R^8 is $-NHR^{13}$ where R^{13} is hydrogen, C_1 - C_{10} alkyl, C_1 - C_{10} alkyl interrupted by 1 to 3 hetero atoms, $-COR^{14}$ where R^{14} is hydrogen, C_1 - C_{10} -alkyl or C_1 - C_{10} -alkyl interrupted by 1 to 3 hetero atoms, or R^{13} is $-C(=NH)R^{17}$, $-SOR^{17}$ or $-SO_2R^{17}$ where R^{17} is C_1 - C_{10} -alkyl or C_1 - C_{10} -alkyl interrupted by 1 to 3 hetero atoms, R^9 is hydrogen, R^{10} is $-OR^{18}$ where R^{18} is hydrogen, C_1 - C_4 -alkyl or C_1 - C_4 -alkoxy- C_1 - C_4 alkyl, p and q are each 1 and r is zero.

12. A compound according to claim 11, in which Ar is a group of formula XV



XV

13. A compound according to any one of the preceding claims, in which R^1 is hydroxy.

14. A compound according to any one of the preceding claims in which R^2 and R^3 are each independently hydrogen or C_1 - C_4 alkyl.

15. A compound according to claim 6, in which R^2 and R^3 are each hydrogen.

16. A compound according to any one of the preceding claims, in which R^4 , R^5 , R^6 and R^7 are each hydrogen or are such that the benzene ring to which they are attached is symmetrically substituted.

17. A compound according to claim 16, in which R^4 and R^7 are identical and are each hydrogen, C_1 - C_4 -alkyl or C_1 - C_4 -alkoxy, and either R^5 and R^6 are identical and are each hydrogen, C_1 - C_4 -alkyl, C_1 - C_4 -alkoxy or C_1 - C_4 -alkoxy- C_1 - C_4 -alkyl, or R^5 and R^6 together denote $-(CH_2)_s-$ or $-O(CH_2)_tO-$ where s is 3 or 4 and t is 1 or 2.

18. A compound according to claim 1, in which Ar is a group of formula III, IV, V, XII or XV, R^1 is hydroxy, R^2 and R^3 are hydrogen, and R^4 and R^7 are identical and are each hydrogen, C_1 - C_4 -alkyl or C_1 - C_4 -alkoxy, and either R^5 and R^6 are identical and are each hydrogen, C_1 - C_4 -alkyl, C_1 - C_4 -alkoxy or C_1 - C_4 -alkoxy- C_1 - C_4 -alkyl, or R^5 and R^6 together denote $-(CH_2)_4-$ or $-O(CH_2)_2O-$, in free or salt or solvate form.

19. A compound according to claim 18, in which the carbon atom in formula I marked with an asterisk * has the R configuration.

20. A compound according to any one of the preceding claims, substantially as described in any one of the Examples.

21. A pharmaceutical composition comprising a compound according to any one of the preceding claims, optionally together with a pharmaceutically acceptable carrier.

22. Use of a compound according to any one of claims 1 to 20 for the preparation of a medicament for the treatment of a condition which is prevented or alleviated by activation of the β_2 -adrenoreceptor.

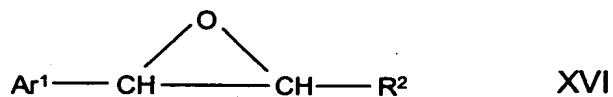
23. Use of a compound according to any one of claims 1 to 20 for the preparation of a medicament for the treatment of an obstructive or inflammatory airways disease.

24. Use according to claim 22 or 23 in conjunction with an anti-inflammatory drug substance.

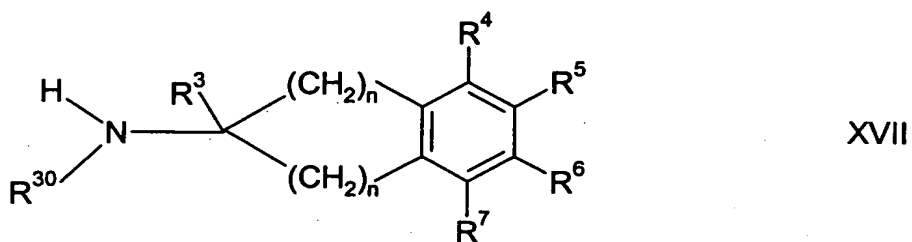
25. A process for the preparation of a compound of formula I in free or salt or solvate form comprising:

(a) for the preparation of a compound where R^1 is hydroxy, either

(i) reacting a compound of formula

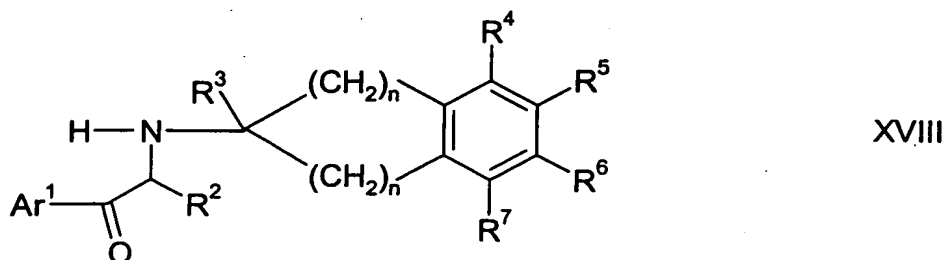


with a compound of formula



where Ar^1 is Ar as defined in claim 1 or a protected form thereof, R^2 , R^3 , R^4 , R^5 , R^6 , R^7 and n are as defined in claim 1 and R^{30} is hydrogen or an amine-protective group, or

(ii) reducing a compound of formula



where Ar^1 is Ar as defined in claim 1 or a protected form thereof, R^2 , R^3 , R^4 , R^5 , R^6 and R^7 are as defined in claim 1, to convert the indicated keto group into $-\text{CH}(\text{OH})-$; or

(b) for the preparation of a compound where R^1 is hydrogen, reducing a corresponding compound of formula I where R^1 is hydroxy; or

(c) for the preparation of a compound of formula I where R^1 is alkoxy, O-alkylating a corresponding compound of formula I where R^1 is hydroxy;

and, optionally, converting a resultant compound of formula I in protected form into a corresponding compound in unprotected form;

and recovering the resultant compound of formula I in free or salt or solvate form.
